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(to be used for all correspondence after initial filing)

Application Number 08/397,225

Filing Date March 28, 1995

First Named Inventor Pericaudet

Group Art Unit 1632

Examiner Name S. Priebe

Attorney Docket Number EX 93015

Total Number of Pages in This Submission

ENCLOSURES (check all that apply)

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Certified Translations of FR 93 08596 and FR 94 04590. |
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Remarks

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David J. Kulik, Wiley Rein & Fielding, LLP

Signature

Date

November 27, 2001

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RECEIVED PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Michel PERRICAUDET *et al.*

Appl. No.: 08/397,225

Filed: March 28, 1995

For: DEFECTIVE ADENOVIRUS VECTORS
AND USE THEREOF IN GENE
THERAPY

Art Unit: 1632

Examiner: S. Priebe

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NOV 30 2001
TECH CENTER 1600/2900Commissioner for Patents
Washington DC 20231**Submission of Certified English Translations**
Perfecting Applicants' Claim to Priority to FR 93 08596 and FR 94 04590

Applicants hereby submit certified translations into the English language of the two French priority applications FR 93 08596, filed July 13, 1993, and FR 94 04590, filed April 18, 1994. The Patent Office previously mentioned these translations (*see* Office Action of April 28, 1998). The claim to priority to these French documents is indicated in the Declaration filed March 28, 1995, and the U.S. Elected Office received the two priority documents (*see* Notification of Missing Requirements dated April 4, 1995). Applicants' claim to the benefit of these two priority documents is now perfected. Applicants explain below the support for the allowable claim 42, newly added in the Amendment filed November 16, 2001.

No fees, extensions of time, petitions, or requests are believed to be necessary to enter or consider this paper and the attached papers. If, however, any fees, extensions of time, petitions, or requests are required in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions, requests, or petitions necessary and the Commissioner is hereby authorized to charge Deposit Account # 50-1129 for any fees.

Remarks

A review of the contents of these English translations shows that allowable claim 42, and the related subject matter discussed below, finds support in both of the French priority documents. For example, applicants disclose how to make and use the claims reciting a recombinant adenovirus having deletions in, and thus non-functional E1, E2, and/or E4 regions, or the genes or ORFs in these regions, through at least the introduction to Example 4 (page 17, lines 1-6 of the English translation of FR 93 08596, and page 17, lines 4-8 of the English translation of FR 94 04595). That section of each of the French documents reads:

This example describes the construction of complementing cell lines for the E1, E2, and/or E4 regions of adenovirus. These cell lines permit the construction of recombinant E1, E2, and/or E4 region-deleted adenoviruses according to the invention, without the use of helper virus. These viruses are obtained by in vivo recombination, and may contain major heterologous sequences.

Thus, each of the two French priority applications explicitly discloses and describes how to make a recombinant adenovirus where different combinations of the E1, E2, and/or E4 regions are deleted or rendered non-functional. Also, each document discloses and describes complementing cell lines that contain E1, E2, and/or E4 regions or genes of those regions (*see also* the cell lines 1 to 8 listed at pages 17 to 18 of each document). Accordingly, both the recombinant adenoviruses and the complementing cell lines used to supply the functions from the deleted or non-functional E1, E2, and/or E4 regions are disclosed.

Furthermore, at least this same section of each document indicates what one of skill in the art would clearly understand from the entire content of these documents - that producing the complementing cell line having one or more adenovirus genome regions or genes indicates that a corresponding adenovirus can be produced that is deleted or non-functional in the same one or more regions or genes. Logically, then, a disclosure of the deleted adenovirus is also a disclosure of the complementing cell line used to produce it, and a disclosure of a complementing cell line is also a disclosure of the deleted adenovirus it can produce. One of skill in the art also understands from the content of the French priority documents that rendering these E1, E2, and/or E4 regions non-functional or deleting them from an adenovirus creates a

replication-defective adenovirus (*see, for example*, the claims and page 3 of these documents). In addition, the comments below show combinations of early regions that can be complemented for in producing a replication-defective adenovirus through the use of a transformed cell line. These combinations include those comprising the E1 and E2A regions, the E1 and E4 regions, and the E2A and E4 regions. The clear reason for complementation through a cell line would be to provide adenoviral functions not present in a replication-defective adenovirus.

To more clearly demonstrate the content of the French priority documents, applicants refer to the list of several recombinant adenoviruses (*see* English translation of FR 93 08596 at page 13, lines 24-29, and page 14, lines 11-14; *also* English translation of FR 94 04595 at page 13, lines 25-31, and page 14, lines 14-17) along with the list of several complementing cell lines (*see* English translation of French application 93 08596, at page 17, line 23 through page 18, line 6; and English translation of FR 94 04595 at page 17, line 27 through page 18, line 10). In addition to other parts of these documents, these lists provide explicit, literal support for the concept above - recombinant adenoviruses having different combinations of E1, E2, and/or E4 regions deleted or rendered non-functional can be complemented for using a cell line having deleted regions or genes. Clearly these lists also provide explicit support for how to make and use any of the combinations possible with either the listed adenoviruses, the listed cell lines, or both, in order to produce a replication-defective adenovirus. As referred to above, one reason for producing the cell line to complement a missing adenoviral function is to produce a replication-defective adenovirus from the understanding that the complemented function is used or required by the adenovirus in the replication process. Thus, producing the recombinant adenovirus or complementing cell line incorporates the knowledge that the complementation for the E1, E2, and/or E4 regions, or combinations of these regions, is for the purpose of preparing replication-defective adenovirus in a cell line.

For the Examiner's convenience, applicants submit below two tables that contain the recombinant adenoviruses and complementing cell lines listed in the French priority documents at the pages noted in the paragraph above. Next to each listed adenovirus or each listed cell line having adenoviral genome sequences is the early region(s) deleted or rendered non-functional, in the case of the adenoviruses (first table), or contained in the complementing cells in the case of cell lines (second table).

Example 1 recombinant or mutant adenovirus (copied directly from FR 93 08596 and FR 94 04595)	early regions deleted or non- functional (from restriction map and/or map units)
mt1: Ad5 fragment 0-20642(SauI) ligated to (SauI)33797-35935	E2A E3 E4
mt2: Ad5 fragment 0-19549(NdeI) ligated to (NdeI)31089-35935	E2A E3
mt3: Ad5 fragment 0-10754(AatII) ligated to (AatII)25915-35935	E2A & B
mt4: Ad5 fragment 0-11311(MluI) ligated to (MluI)24392-35935	E2A & B
mt5: Ad5 fragment 0-9462(SalI) ligated to (XhoI)29791-35935	E2A & B E3A & B
mt6: Ad5 fragment 0-5788(XhoI) ligated to (XhoI)29791-35935	E2A & B E3A & B
mt7: Ad5 fragment 0-3665(SphI) ligated to (SphI)31224-35935	E2A & B E3
mt8: 0-4623(ApaI) from Ad RSV β Gal ligated to Ad5 (ApaI)31909-35935	E1 E2A & B E3
mt9: 0-10178 (BglII) from Ad RSV β Gal ligated to (BamHI) 21562- 35935	E1 E2B

293-derived cell lines of Example 4 (copied directly from FR 93 08596 and FR 94 04595)	complementing Ad genes in cell lines
1. 293 cells having the 72K gene of the E2 region of Ad5 under the control of the LTR of MMTV	E2A
2. 293 cells having the 72K gene of the E2 region of Ad5 under the control of the LTR of MMTV and the gene for the glucocorticoid receptor	E2A
3. 293 cells having the 72K gene of the E2 region of Ad5 under the control of the LTR of MMTV and the E4 region under the control of the LTR of MMTV	E2A E4
4. 293 cells having the 72K gene of the E2 region of Ad5 under the control of the LTR of MMTV, the E4 region under the control of the LTR of MMTV and the gene for the glucocorticoid receptor	E2A E4
5. 293 cells having the E4 region under the control of the LTR of MMTV	E4
6. 293 cells having the E4 region under the control of the LTR of MMTV and the gene for the glucocorticoid receptor	E4
7. gm DBP6 cells having the E1A and E1B regions under the control of their own promoter	E1A E1B
8. gm DBP6 cells having the E1A and E1B regions under the control of their own promoter and the E4 region under the control of the LTR of MMTV	E1A E1B E4

As one of skill in the art would understand, late region ORFs or genes that are contained on the opposite strand of the adenovirus may also be deleted in the particular examples of the lists (not listed here).

From the information explicitly shown in the French priority documents, one of skill in the art understands that various combinations of E1, E2, and E4 regions, at least, can be deleted from an adenovirus and/or inserted into a complementing cell line for the purpose of complementing the deleted, replication functions of the adenovirus. Applicants note that one of skill in the art recognizes that the 72K gene or protein of the E2 region, noted throughout the two French priority documents, corresponds to and/or is the same as the E2A region of the E2 region (*see, for example*, page 930, Figure 24-22, of enclosed excerpt of Watson *et al.* (eds.), *Molecular Biology of the Gene*, 4th Ed., Addison Wesley & Benjamin Cummings, Chap. 24, showing E2A region as encoding the 72 K DNA binding protein; *citing* Tooze (ed.), *Molecular Biology of Tumor Viruses: DNA Tumor Viruses*, 2d Ed., Cold Spring Harbor Press, 1981). The two French priority documents specifically note that this E2A region (or "72K protein") is particularly

suitable for deletion, mutation, or being rendered non-functional in an adenovirus and for inserting into a complementing cell line (*see, for example*, English translation of FR 93 08596 at page 10, lines 9-10, page 17, lines 24-32). Accordingly, applicants' allowable claim 42 and the subject matter reciting a recombinant adenovirus that requires complementation of or is non-functional in the E1, E2A, and E4 regions, or combinations of any two of these regions, as well as related subject matter, find support in both of the French priority documents. For example, each of the combinations comprising deletions in or non-functional E1 + E2A regions, E1 + E4 regions, and E2A + E4 regions, are specifically represented by one of more of the adenoviruses or cell lines of the tables.

The right panels of these tables can be produced by comparing the listed restriction sites and/or nucleotide base positions, which were taken directly from the French priority documents, to the disclosed maps of Adenovirus (*see* Figures 1, 2, and 3 of the French priority documents), to publicly available maps and analysis of the Adenovirus genome (*see, for example*, page 930, Figure 24-22, of enclosed excerpt of Watson *et al.* (eds.), *Molecular Biology of the Gene*, 4th Ed., Addison Wesley & Benjamin Cummings, Chap. 24; and Berkner, *BioTechniques* 6:616-629 (1988)), or to the publicly available sequence of Ad5 genome (*see* Chroboczek *et al.*, *Virology* 186:280-285 (1992), referring to GenBank accession number M73260).

One of the ways to correlate applicants' nucleotide base positions in the tables above to specific early gene regions and the published reports is through the use of genome map units. Many of the Adenoviral (Ad2 or Ad5 serotypes) genome maps contain a 1 through 100 scale referring to these map units. As specifically noted in Berkner *et al.* (at Figure 1, page 618, and the comments there referring to Ad2 and Ad5), each unit in the 1-100 map unit scale commonly used corresponds to 360 base pairs. Therefore, one can compare the map from Figure 24-22 of Watson, noted above, with the mt3 deletion mutant listed in the first table above. The mt3 adenovirus refers to a deletion between 10754 and 25915. This deletion corresponds to 29.87 map units [$10754 \div 360$] through 71.99 map units [$25915 \div 360$]. According to the map from Watson, for example, the Adenovirus genome between map units 29.87 and 71.99 includes the E2A region. Thus, the mt3 adenovirus contains a non-functional or deleted E2A region, as noted in the right panel ("early region deleted") of the first table. Each of the deletions or restriction

fragments noted in the tables can be correlated to early gene adenoviral regions in the same way. The Ad RSV β Gal recombinant adenovirus is discussed in Stratford-Perricaudet *et al.*, *J. Clin. Invest.*, 90:626-630 (1992)(copy enclosed), showing the deletion in the E1 region.


Applicants respectfully submit that the subject matter of allowed claim 42 added in the Amendment filed November 16, 2001, and the subject matter relating to adenoviruses and complementing cell lines employing any combination of two of the E1, E2A, and E4 regions, find specific support in each of the two French priority documents. Thus, combinations comprising deletions or non-functional E1 + E2A regions, E1 + E4 regions, and E2A + E4 regions, find support in the French priority documents. These same documents also disclose how the complementing cell lines with the same regions or combinations of regions complement a replication function in a replication-defective adenovirus. If a telephone conference with applicants' representative would further the Examiner's review of the documents submitted, the Examiner is invited to call at the number provided below.

The Commissioner is hereby authorized to charge any fee required to enter or consider this paper, or consider any document submitted with this paper, or keep this application pending, to Deposit Account No. 50-1129.

Respectfully submitted,
WILEY REIN & FIELDING LLP

Date: November 27, 2001

By:



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Enclosures: Certified translation into English language of FR 93 08596
Certified translation into English language of FR 94 04590
excerpt of Watson *et al.* (eds.), *Molecular Biology of the Gene*, Chap. 24
Berkner *et al.*; Chroboczek *et al.*; Stratford-Perricaudet *et al.*